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September 30, 1999

BY COURIER

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 99D-1738

Dear Sir or Madam:

Please find enclosed two originals and one copy of the comments of The International Pharmaceutical Aerosol Consortium ("IPAC") on the FDA's draft *Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action,* dated June 1999 (the "Draft Guidance"). Please file the original copies and time/date stamp the photocopy and return it to the messenger.

We greatly appreciate the Agency's flexibility in allowing us extra time to review and comment on the Draft Guidance (as discussed via email on August 26, 1999 with Dr. Wallace Adams, Office of Pharmaceutical Science, CDER/FDA).

Thank you for your consideration.

Sincerely,

Mary Devlin Capizzi

Mary Devlin Capizzi

Enclosure

99D-1738

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COMMENTS

on a draft Guidance for Industry
Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action

Submitted by
The International Pharmaceutical Aerosol Consortium

September 30, 1999

I. INTRODUCTION

The International Pharmaceutical Aerosol Consortium (IPAC) is an association of companies that develop and manufacture oral inhalation and intranasal products for local and systemic treatment of chronic obstructive pulmonary disease (COPD), rhinitis, and migraine. These comments are being submitted on behalf of the following members of IPAC's Working Group on FDA Guidance: Aradigm, AstraZeneca, Boehringer Ingelheim, Dura Pharmaceuticals, Eli Lilly, GlaxoWellcome, Inhale Therapeutic Systems, Inc., Medeva Americas, Pfizer, Rhône-Poulenc Rorer, Schering-Plough Corporation and 3M Pharmaceuticals. The members of the IPAC Working Group on FDA Guidance are committed to the highest standards of safety, efficacy and quality in the development and manufacture of drug products for oral inhalation and intranasal delivery.

The member companies of the IPAC Working Group on FDA Guidance commend the Oral Inhalation and Nasal Drug Products Technical Committee, the Locally Acting Drug Products Steering Committee, the Biopharmaceutics Coordinating Committee and the Inhalation Drug Products Working Group of the Chemistry, Manufacturing, and Controls Coordinating Committee, in the Center for Drug Evaluation and Research (CDER), on their efforts to develop this Draft Guidance for Industry. The IPAC Working Group also appreciates the opportunity to provide the following comments to the Agency.

Patients rely on nasal spray medications and inhalation solutions and suspensions for the safe and effective treatment of diseases. The Food and Drug Administration (FDA) and the pharmaceutical industry each strive to respond to the needs of patients for these medications by expediting the availability of new products while maintaining appropriate standards of safety, efficacy and quality. We hope that through our comments we may assist the Agency in developing a final Guidance that will assist developers in measuring bioavailability (BA) and establishing bioequivalence (BE) in support of new or abbreviated drug applications for locally acting drugs in nasal aerosols and nasal sprays.

II. GENERAL COMMENTS

- We are encouraged that the Draft Guidance recognizes the challenges and difficulties of demonstrating equivalence of nasal sprays and inhalation therapies, particularly of corticosteroids intended for local action.

- We strongly support application of the same standards to ANDAs and NDAs, as product quality, safety and efficacy considerations are independent of the regulatory mechanism for approval.

- We agree that systemic pharmacokinetic (PK) and pharmacodynamic (PD) data alone are not sufficient to determine bioequivalence for nasal solution and suspension drug products that are locally acting.

- We agree that test products should be qualitatively (Q1) the same and quantitatively (Q2) essentially the same as the reference product, and that test products should mirror the container closure system of the reference product.

- We recommend that requirements for in vivo and in vitro testing for BE approval of all nasal products be the same and include in vitro pharmaceutical equivalence, systemic exposure and local delivery.

- In light of the expected revisions to 21 CFR 314.70, we believe that the Postapproval Change section is beyond the scope of this Draft Guidance and should be deleted.

- We note that the Draft Guidance does not provide guidance on in vivo bioequivalence standards, and therefore a second version of the Draft Guidance should be reissued, with another opportunity for public comment when such guidance is available.

III. BA/BE TESTING OF NASAL SOLUTION PRODUCTS SHOULD INCLUDE IN VIVO MEASUREMENTS

The Draft Guidance relies on in vitro methods only for BA and BE testing of locally acting solution nasal drug products. The Draft Guidance notes the questionable clinical relevance of in vitro methods, but nevertheless recommends exclusive reliance on in vitro methods to access BA and BE in nasal solution drug products. We believe that the Draft Guidance includes a number of erroneous assumptions upon which it relies in drawing its conclusion that exclusive reliance on vitro methods is sufficient. Following are two examples of such assumptions:

- ***Assumption: "Equivalent in vitro performance assures bioequivalence."***

  To base the entire BE approval of any nasal solution product solely upon in vitro criteria is flawed unless there is sufficient in vivo correlation to establish the predictability and objectivity of the tests. Clinical relevance of the proposed in vitro tests for nasal products has not yet been established. A major concern with relying upon in vitro data as the sole basis for any BE assessment is the lack of objectivity of the in vitro tests.

- ***Assumption: "In vitro studies would be more sensitive than clinical studies."***

  This assumption ignores the ability to perform BE pharmacokinetic studies on nasal corticosteroid products, including budesonide, flunisolide, and triamcinolone acetonide. There is no apparent reason why well-designed pharmacokinetic and pharmacodynamic studies should be attributed less weight than in vitro experiments. Similarly, there is no apparent reason why a well-designed clinical study for local delivery, such as a clinical trial with both placebo and active treatment reference product controls, should be given less weight than in vitro experiments.

Given that there is no scientific basis to conclude that the current in vitro tests are *a priori* more sensitive BE measures than clinical trials and that these in vitro tests are adequate to produce quality BA and BE results for nasal solution products, we propose that a scientifically justifiable BE/BA testing program be applied to both nasal solution and suspension formulations. In particular, we propose that:

- product quality BA and BE testing program include:

  1) the in vitro methods included in the Draft Guidance,

2) the systemic exposure study, and
3) the local delivery study;

- all three types of testing be required of all nasal products, and not just suspension products; and

- approval criteria would require that statistical BE tests be met for all three analyses.

The improvements suggested above would resolve the inconsistencies in the Draft Guidance and provide fair and objective approval criteria for all nasal products.

IV. IN VITRO TESTS

In Vitro Measurements Must be Appropriate and Clinically Relevant

The in vitro aspects of the Draft Guidance are in a relatively advanced state of development compared to the in vivo sections of the document, however, there is no evidence that the in vitro measures selected are appropriate and clinically relevant. This gives cause for concern should these requirements become mandatory for characterizing and demonstrating equivalence of innovator or generic products subject to minor manufacturing changes.

Equivalence of the Container and Closure System

The container and closure system is an intimate part of the dose form and influences how much drug will be delivered and where drug will be delivered. The Draft Guidance should therefore specifically require equivalence of all critical dimensions of the container and closure system of the test and reference products.

Reliance Upon In Vitro PSD Methods

The Draft Guidance assumes that in vitro PSD methods can measure product quality BA and BE and are more sensitive and discriminating than in vivo methods. Compared to in vitro methods, clinical endpoints may be more variable and relatively insensitive in detecting differences between products; however, this observation alone is insufficient to justify reliance upon even more problematic in vitro methods. For example:

- Available PSD test methods for nasal products have significant shortcomings as BA and BE metrics. The "throats" or inlet of the preferred Multistage Cascade Impaction (CI) and the Multistage Liquid Impinger (MSLI) in vitro PSD tests have been developed for oral inhalation products and bear no relationship to the anatomy of the nose. The test inlet flow velocity has also been developed for oral inhalation products; however, this velocity is different for products given to the nose.

- The stages selected for the PSD analysis are appropriate for oral inhalation, but these particle-sizing stages have not been optimized for nasal delivery. Current data indicates that larger sized particles, greater than 10 microns, are preferable for nasal bioactivity. As acknowledged on page 13 of the Draft Guidance, this is precisely the size range where the available CI and MSLI in vitro tests are the least precise and the least useful, as these tests do not size particles greater than 10 microns.

Batch Requirements in the Draft Guidance are Inappropriate

Section A on page 8 of the Draft Guidance, which pertains to batches and drug product sample collection, contains batch requirements that are inappropriate for a product quality BE assessment. Because of the critical nature of this testing in the BE assessment, and because of the limited number (three) of batches examined, it is appropriate and fair to require three production-scale batches of the test product, as well as the reference product. If the stability tests or the clinical studies on the test product were done with smaller-sized lots, then these should be tested and included in the comparison as well. Batches should represent production scale and process, container closure system, and active drug substance.

Control of Extractables Should be Consistent for Test and Innovator Products

In light of the Agency's requirements for characterizing the impurities and extractables in the components of the container and closure system of the innovator product to ppm and ppb levels, extractables should be controlled in the components of the test product to the same levels. The requirements for controlling extractables in all components of the container and closure system should be specified in the Draft Guidance, precisely as they are specified in the *Draft Guidance For Industry: Metered Dose*

Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products, Chemistry, Manufacturing and Controls.

V. LOCAL DELIVERY STUDIES

BE Assessments of Local Delivery

The Draft Guidance attempts to describe appropriate designs for local delivery studies. To facilitate BE assessments of local delivery, however, the Draft Guidance should provide more flexibility for the sponsor to choose the most appropriate study design. An appropriate BE study with a clinical endpoint to establish equivalent local delivery of drug from test and reference products to the nose should include documentation of the sensitivity of the study design in order to discriminate between differing doses. This documentation typically relies upon the inclusion of a second dose of the reference product and may also include a second dose of the test product. It is appropriate to allow doses to differ by as much as fourfold and to utilize doses outside of the recommended therapeutic range to increase study sensitivity.

To properly differentiate product-related findings from those occurring by chance, it is critical that a placebo treatment be included in any local delivery BE study. Such a trial, containing test and reference products and placebo, has recently been published for a test nasal formulation of beclomethasone dipropionate (*See* Casale TB, Azzam SM, Miller RE, Oren J (1999), *Demonstration of therapeutic equivalence of generic and innovator beclomethasone in seasonal allergic rhinitis*, SAR Study Group, *Ann Allergy Asthma J 82*: 435-441, (Study design had the sensitivity to conclude local delivery BE for the test and reference nasal products)).

BE Requirements for Local Delivery for Seasonal Allergic Rhinitis

The Draft Guidance proposes on page 18 that fulfilling the BE requirements for local delivery for seasonal allergic rhinitis (SAR) is sufficient to grant the sponsor of the test product all the indications in the reference product labeling. This proposal does not seem scientifically justifiable in light of the uncertainties of the particle size distributions of test and reference products. The test product might pass a SAR clinical test, yet would fail the second indication test if this were studied.

VI. STUDIES OF SYSTEMIC EXPOSURE AND SAFETY

Study Design Should be Sensitive to Differing Doses

An appropriate BE study with a pharmacokinetic or pharmacodynamic endpoint to establish equivalent systemic exposure of drug from test and reference products to the nose should include documentation of the sensitivity of the study design to discriminate between differing doses. This documentation typically relies upon the inclusion of a second dose of the reference product and may also include a second dose of a test product.

BE Standards Should be Clinically Relevant

We agree that PK and PD studies to assess the effects of a drug on HPA-axis should be performed and are helpful in characterizing the systemic exposure of locally active compounds. These studies, however, may not serve as adequate indicators to assess all of the potential systemic effects. We strongly support the appropriate use of the systemic study as one component of the BE assessment (other components are in vitro testing and local delivery study). It must be recognized that PK and PD testing alone are not sufficient to justify substitutability of one product for another.

The substitutability of products is of particular relevance to pediatric and geriatric patient populations, where the potential to effect growth velocity or fragile/broken bones, respectively, is magnified. The FDA, in its *Class Labeling for Intranasal and Orally Inhaled Corticosteroid Containing Drug Products*, acknowledges that a reduction in growth velocity in pediatric patients has been observed in the absence of laboratory evidence of HPA-axis suppression, and suggests that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. We believe that the Draft Guidance, in providing BE guidance for systemic exposure, should require validated study models to document equivalent systemic safety (especially if it is a pharmocodynamic model).

Pediatric Use of Drug Products Should be Considered

The Draft Guidance does not consider the required BE testing for nasal products administered to children. As it is well established that children metabolize and react to many drugs differently than adults, it is not appropriate to assume that BE results generated in adults apply equally well to children. For nasal products in particular, care must be exercised when extrapolating to the pediatric population because children

breathe at a different rate, have a different airflow, and potentially different nasal drug deposition because of the smaller size of the airway passages compared with adults. A proposed BE testing program in children, including at least a systemic exposure study for safety, is needed.

VII. THE GUIDANCE REQUIRES FURTHER DEVELOPMENT

Guidance on BE Statistical Standards Needed

The statistical requirements in the Draft Guidance, including the proposed upper limits for concluding BE for the in vitro, local delivery and systemic exposure assessments, are incomplete. In particular, no in vivo BE standards are provided. Section IX.E of the Draft Guidance, which is under development, is absent from the document. In addition, a significant portion of Section IX.B.2.b was not made available to industry until August 16, 1999. We strongly recommend that the Draft Guidance be reissued as a second draft when such statistical procedures and definitions are available, and a second period of public comment be required before this Draft Guidance may be finalized.

Consistency with Other Guidances

We recommend that a stronger link be created between the development tests described in the Draft Guidance and the in vitro tests described in the companion *Chemistry, Manufacturing and Controls (CMC) Draft Guidances For Industry: Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products, and Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products.*

We also suggest that the Postapproval Change section be deleted from the Draft Guidance. In light of the collaborative process undertaken by industry and the Agency in developing the SUPAC guidances, and the expected revisions to 21 CFR 314.70, we believe a section addressing Postapproval Change is beyond the scope of this Draft Guidance.

VIII. CONCLUSION

We support the Agency's efforts to develop guidance on product quality BA and BE studies for nasal aerosols and nasal sprays and appreciate the Agency's openness to accept public comments on the current Draft Guidance. We also commend the Agency for initiating a discussion on BA and BE studies at the *AAPS/FDA/USP Workshop on*

Regulatory Issues Related to Drug Products for Oral Inhalation and Nasal Delivery, held on 3-4 June 1999 in Washington, D.C. We note, however, that since the *Draft Guidance for Industry Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* was first made available at the June Workshop, the Workshop did not provide the opportunity for meaningful review and discussion of the Draft Guidance. Further, the Draft Guidance, as currently published, is incomplete. The Draft Guidance does not provide guidance on in vivo bioequivalence standards, and must be revised to incorporate certain statistical procedures and definitions.

We believe that a second draft of the *Guidance for Industry Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* should be issued prior to finalization of the Guidance. We reiterate our position that the revised Draft Guidance should require that in vivo and in vitro testing for BE approval criteria of all nasal products be identical and include in vitro pharmaceutical equivalence, systemic exposure and local delivery.

We also suggest that the Agency utilize a technical process to assemble the best available medical, pharmaceutical and academic expertise, from within and outside the FDA, to further address BA and BE studies and make recommendations for a revised draft Guidance. We believe that such a technical process is critical to the future development of nasal sprays and nasal aerosols. We are strongly encouraged by the Agency's recent decision to create an expert panel that will evaluate further CMC and BA/BE issues, and we acknowledge that the creation of an expert panel may be a first step in a necessary technical process.

We hope our comments will be of value to the Agency and we look forward to the publication of a revised Draft Guidance that will effectively serve the current and future needs of the inhalation drug product industry.